

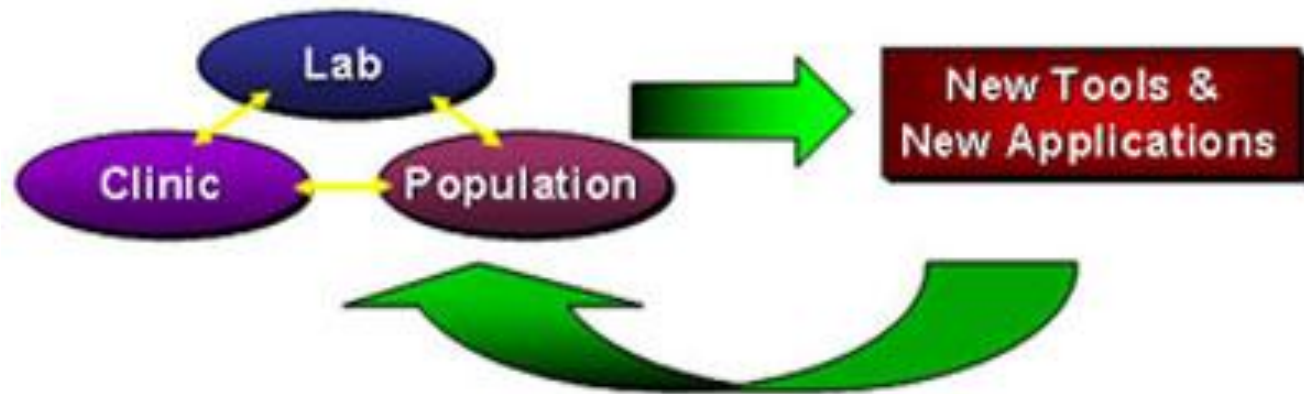
Support for Basic and Translational Breast Cancer Research from the NCI and NIH

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Translational Research

"Translational research transforms scientific discoveries arising from laboratory, clinical, or population studies into clinical applications to reduce cancer incidence, morbidity, and mortality."



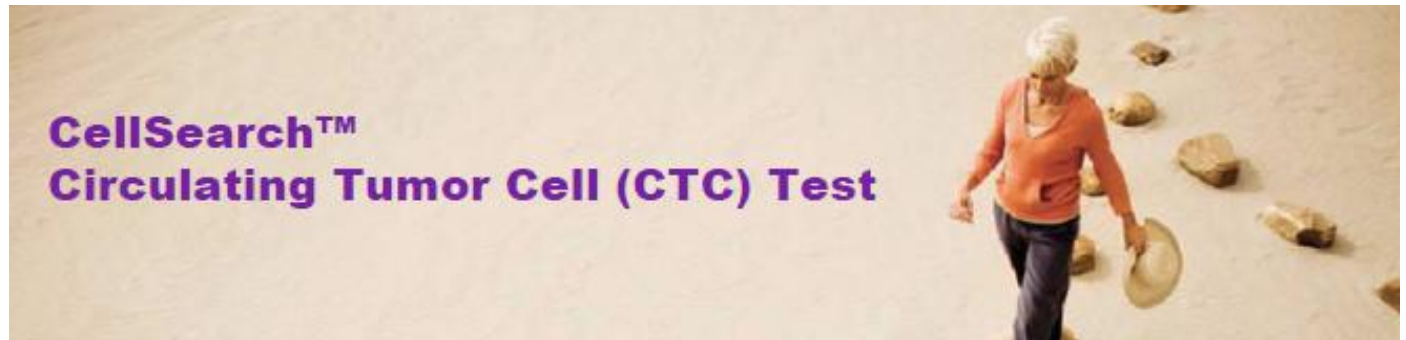
Translational Research

- Has an impact on the lives of breast cancer patients and those at risk for breast cancer
 - New treatments: more effective surgery, radiotherapies, drugs and immunotherapies
 - New diagnostics: imaging modalities and clinical biomarker assays
 - New preventive strategies: lifestyle alterations, chemopreventive agents

Basic Research ≠ Translational Research

- Meets a clinical need
- Requires multi-disciplinary teamwork:
 - Biology, Engineering, Bioinformatics
 - Oncology, Pathology
 - Clinical research methods: statistics and logistics!
 - Randomized trials
 - Epidemiology/Population sciences
- Requires partnerships: academia, government, small business, large business
- Requires time and a LOT of hard work!!

Case study: circulating tumor cells



Case study: circulating tumor cells

- What are CTCs?
 - Cells originating in a primary solid tumor that are detected in the bloodstream...
 - Dying cells?
 - Precursors of metastasis??
 - Cancer stem cells??
 - Self-seeding for primary tumor??

What use are they?

- In early stage breast cancer, to predict likelihood of recurrence after treatment
- In advanced stage cancer, to predict the course of disease
- In advanced disease, to monitor response to therapy

What are CTCs? It all depends...

- Where do you look?
 - Bone marrow?
 - Peripheral blood?
- How do you recognize them?
 - Epithelial cell markers?
 - Breast-specific markers?
 - Tumor-specific markers?
- How do you detect and count them?
 - Unbiased scanning methods?
 - Enrichment via positive selection?
 - Enrichment via negative selection?

Before 2000: lots of research, but...

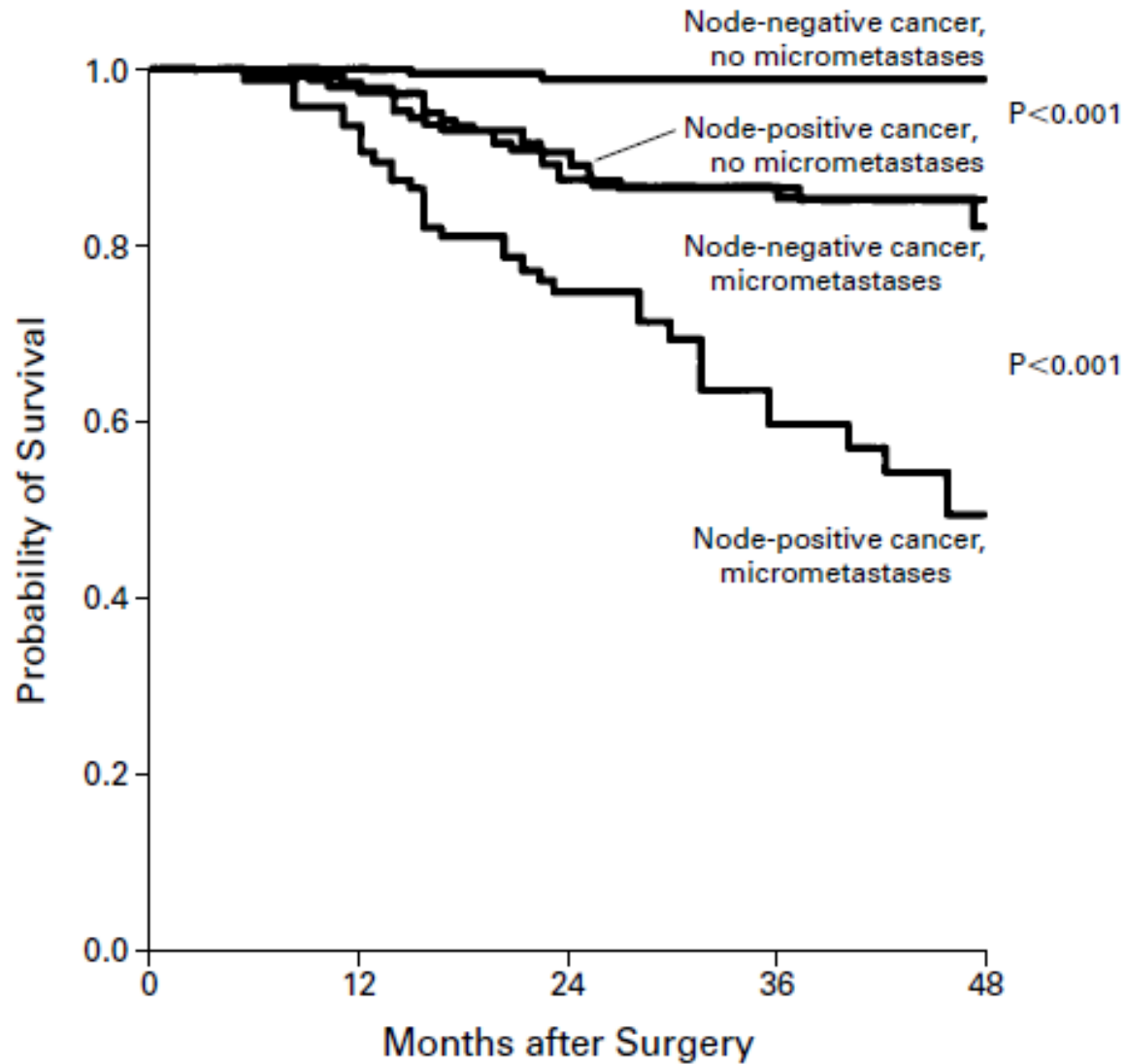
- Multiple small studies, primarily of bone marrow
- Multiple detection strategies, primarily using Abs
- Wide range of values reported for prevalence
- Mostly impossible to compare results between labs
- → NO clear picture!

Clinical advance: Braun et al., 2000

- Bone marrow from 552 patients (stage I-III breast cancer), 191 controls
- 2×10^6 cells stained with anti-cytokeratin mAB, assessed visually
- CK+ cells found in 199/552 (36%) of cases vs 2/191 (1%) of controls
- CK+ status unrelated to nodal status: CK+ cells found in 33% of N0 cases

– Braun et al., 2000. New England J. Med.342:525

Braun et al., 2000



Technical advances

- Ferrofluid: small magnetic particles conjugated to antibodies
- Preservative: enables overnight shipment of samples from multiple sites to a central laboratory

CellSearch® device

- CellSave tube with 7.5 ml blood →
- Capture with EpCAM-ferrofluid →
- Semi-automated flow cytometric analysis
- CTC defined as:
 - Nucleated cell (DAPI positive)
 - Cytokeratin 19-positive
 - CD45-negative

From the Veridex website:

The CellSearch™ System

Blood is collected into a CellSave Preservative Tube and sent to a laboratory for processing



The sample, along with the CellSearch™ Test reagents and controls are placed on the CellTracks® AutoPrep® System



CellSearch™ Circulating Tumor Cell Kit



CellSearch™ Circulating Tumor Cell Control Kit

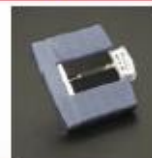
The CellTracks® AutoPrep® System automatically prepares the sample, ready for analysis.



The sample is analyzed on the CellTracks® Analyzer II, and images are presented to the user for classification

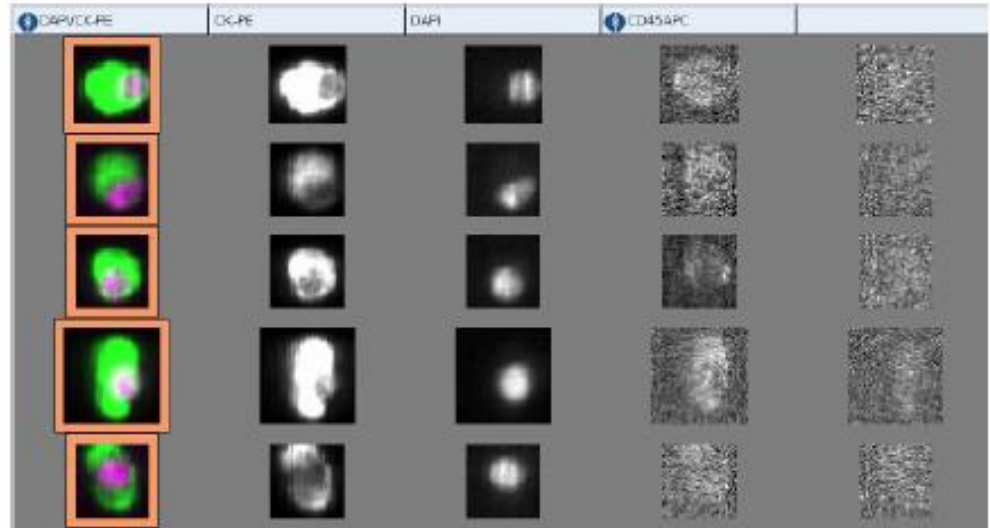


MagNest®



CTC Analysis on the CellSearch® Platform

CTC's
CK-PE+/DAPI+/CD45-APC-



Leucocytes
CK-PE-/DAPI+/CD45-APC+



Analytic validity: Allard et al., 2004

- Analytic validity: how accurately the test detects the analyte(s) of interest
- Multi-center study:
 - Accuracy, sensitivity and linearity of detection in spiked samples
 - Reproducibility across duplicate tubes and multiple operators
 - Prevalence of CTCs in patients with early or late stage solid tumors
 - Allard et al., 2004 Clin. Cancer Res. 10:6897

Clinical Validity

- Clinical validity: how well the test relates to the clinical outcome of interest, e.g., response to therapy, survival, etc.

Clinical Validity: Cristofanilli et al., 2004

- Multicenter prospective study of 177 patients with metastatic BrCa, CTCs measured at beginning of new systemic treatment and 3-4 weeks later.
- A CTC count of 5 or more per 7.5 ml of blood at any time during the course of the disease is predictive of shorter progression-free survival and overall survival.
 - Cristofanilli et al., 2004 New England J. Med. 351:781

FDA Clearance

For *in vitro* diagnostic use.

The CellSearch™ Circulating Tumor Cell Kit is intended for the enumeration of circulating tumor cells (CTC) of epithelial origin (CD45-, EpCAM+, and cytokeratins 8, 18+, and/or 19+) in whole blood.

The presence of CTC in the peripheral blood, as detected by the CellSearch™ Circulating Tumor Cell Kit, is associated with decreased progression free survival and decreased overall survival in patients treated for metastatic breast, colorectal or prostate* cancer. The test is to be used as an aid in the monitoring of patients with metastatic breast, colorectal or prostate cancer. Serial testing for CTC should be used in conjunction with other clinical methods for monitoring metastatic breast, colorectal and prostate cancer. Evaluation of CTC at any time during the course of disease allows assessment of patient prognosis and is predictive of progression free survival and overall survival.

End of story?

- **CLINICAL UTILITY:** whether the results of the test provide information that can contribute to and improve current optimal management of the patient's disease
-???

Clinical Trial: SWOG S0500

- Measure CTCs. Begin chemoRx.
- Arm A: < 5 CTCs \rightarrow F/U for PFS
- If baseline ≥ 5 , measure CTCs at Day 22
- Arm B: < 5 CTCs \rightarrow maintain Rx
- Arm C: \geq % CTCs \rightarrow randomize to current vs. new Rx
- Endpoints: OS, PFS

Future Research Directions

- Increased sensitivity: not all breast cancer CTCs express EpCAM!
- Improved dynamic range
- Enhanced characterization of CTCs
 - Multiple additional labels
 - Functional assays
- Significance of “clumps”
- Role of circulating endothelial cells/endothelial cell precursors

New Technical Approaches

- Immunomagnetic negative selection methods
- Physical approaches (size, density, dielectric properties)
- Optical technologies
- Microfluidics

NCI Grant Support for Basic Research

- Research Project Grant Mechanisms
 - R01 awards (PA-10-068 and others)
 - Program project awards
 - R21 exploratory/developmental grants on selected topics ONLY (many are translational)
 - <http://www.cancer.gov/researchandfunding#fundingopportunities>
- Other NIH institutes (including NIBIB) accept unsolicited R21 applications via PA-10-069

NCI Grant Support for Technology Development

- Innovative Molecular Analysis Technologies (IMAT) Program

<http://innovation.cancer.gov/>

- Cancer Imaging Program

<http://imaging.cancer.gov/>

- Small Business Grants and Contracts (SBIR/STTR programs)

<http://sbir.cancer.gov/>

NCI Multi-Disciplinary Networks for Translational Research

- Specialized Programs of Research Excellence (SPOREs)
<http://spores.nci.nih.gov/>
- Strategic Partnerships to Evaluate Cancer Signatures (SPECS)
<http://www.cancerdiagnosis.nci.nih.gov/>
- Early Detection Research Network (EDRN)
<http://edrn.nci.nih.gov/>

NCI Strategic Initiatives

- The Cancer Genome Atlas
<http://cancergenome.nih.gov/>
- TARGET (Therapeutically Applicable Research to Generate Effective Therapies)
<http://target.cancer.gov/>
- Clinical Proteomic Technologies for Cancer
<http://proteomics.cancer.gov/>
- NCI Alliance for Nanotechnology
<http://nano.cancer.gov/>
- Physical Science-Oncology Centers
<http://physics.cancer.gov/>

NCI Biospecimen Resources

- Co-operative Human Tissue Network
<http://www.chtn.nci.nih.gov/>
- Specimen Resource Locator
<http://cancer.gov/specimens>
- NCI Office of Biorepositories and Biospecimen Science
 - NCI Best Practices for Biospecimen Resources
 - Biospecimen Research Database and funding opps<http://biospecimens.cancer.gov>

Access to NCI Development Services

- NExT: NCI Experimental Therapeutics Development Program
<http://next.cancer.gov/>
- CADP: Clinical Assay Development Program
soon: <http://cadp.cancer.gov>

NIH Support for Biomedical Engineering

- National Institute of Biomedical Imaging and Bioengineering
<http://www.nibib.nih.gov>
 - Bioengineering Research Partnership Grants
 - Quantum Grants program
 - Biotechnology Resource Centers
- NIH Nanotechnology Initiatives
<http://www.nibib.nih.gov/Research/NIHNano>

Advancing Novel Science in Women's Health Research (ANSWHR)

- Advancing Novel Science in Women's Health Research (R21)

<http://grants.nih.gov/grants/guide/pa-files/PAS-10-226.html>

Purpose: To promote innovative, interdisciplinary research to advance women's health research and the study of sex/gender differences across the full range of WHR

Co-ordinated by the Office of Women's Health Research,
NIH Office of the Director

Building Interdisciplinary Research Careers in Women's Health (BIRCWH, K12)

- Institutional Mentored Research Career Development Program Award (K12) for junior faculty (Ph.D. and M.D.)
- Trans-NIH effort, co-sponsors include NCI, NICHD, NIAMS, NIA, NIAAA, NIMH, NIEHS, NIDA, the Office of Dietary Supplement (ODS) and the Agency for Healthcare Research and Quality (AHRQ)
- Four scholars per institution; candidates apply directly to institution, not to NIH
- All types of research from basic, clinical to translational and health services research in women's health
- Salary support to "protect" their research time, ongoing support for 2-5 years
- Annual meeting each year at the NIH to share research findings